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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,604	11/14/2001	Avi J. Ashkenazi	P2730P1C25	1800

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EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,604	GENENTECH, INC.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/4/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Formal Matters

A. The Amendment dated 6/4/04 has been entered into the record.

B. Claims 119-131 were pending in the application. In the Amendment dated 6/4/04 Applicants canceled claims 127 and 128. Therefore, claims 119-126 and 129-131 are pending and are the subject of this Office Action.

C. The Information Disclosure Statement dated 6/4/04 has been entered into the record. All references have been considered.

D. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Priority

A. The effective filing date for claims 119-126 and 129-131 remains 11/14/01. Applicants' arguments rely on the gene amplification assay for patentable utility which was first disclosed in U.S. Provisional Application 60/141,037, filed June 23, 1999, priority to which has been claimed in this application. Therefore, Applicants argue that the present application is entitled to at least the priority date of June 23, 1999. However, this argument is not deemed persuasive as set forth in the below rejection under 35 USC 101.

3. Specification

A. The objection to the specification has been withdrawn in view of Applicants' amendments to the specification to remove all embedded hyperlinks.

B. The objection to the specification has been withdrawn in view of Applicants' amendment to the title to more closely reflect the claimed subject matter.

4. Claim Objections

A. The objection of claims 119-126 and 129-131 has been withdrawn in view of Applicants' amendments to the claims to replace the phrase "shown in Figure 233 (SEQ ID NO:326)" with "of SEQ ID NO:326."

5. Claim Rejections - 35 USC § 101

A. Claims 119-126 and 129-131 remain rejected under 35 USC 101 for the reasons already of record on pages 3-4 of the Office Action mailed 3/9/04. Applicants state that, according to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 USC 101 if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Applicants further state that, under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed and that any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility. Applicants also state that if the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, then a rejection based on utility should not be imposed. The Examiner is not questioning that the present invention is not credible. The issue of "specific" and "substantial" will be discussed below.

Turning to Applicants' arguments, Applicants are relying on the gene amplification data for patentable utility (e.g. specific and substantial, or well-established) for this case. They argue that gene amplification is an essential mechanism for oncogene activation and the assay is well-described in Example 170, page 539 of the present application. The gene amplification data shows that genomic DNA was isolated from a variety of primary cancers and cancer cell lines listed in Table 9 (especially page 554, Table 9C) which includes primary colon cancers of the type and stage indicated in Table 8 (page 546).

These arguments have been considered, but are not deemed persuasive. The present claims are drawn to proteins which are related to PRO1281 whereas these arguments are drawn to genomic DNA which, ultimately, encodes PRO1281. The fact that gene amplification may be an essential mechanism for oncogene activation is, respectfully, not relevant to the present claims which, again, are drawn to proteins. The fact that genomic DNA was isolated from a variety of cancers does not provide a utility for the proteins encoded by the DNA since Applicants have not demonstrated that the increase in genomic DNA would ultimately lead to an increase in protein expression in these cancer cells, which would be required in this situation in order for the proteins of the present invention to have a utility.

Applicants argue that it is generally well-understood in the art that DNA copy number influences gene expression and cite Ornfoft et al., Hyman et al. and Pollack et al. as supporting reference. Applicants also submit a Declaration by Dr. Polakis. This Declaration, which is being treated as a Declaration under 37 CFR 1.132, states that, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in

corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. Therefore, Applicants argue that, given the combined teachings in the art exemplified by Ornoft et al., Hyman et al. and Pollack et al., as well as the Polakis Declaration, one of skill in the art would reasonably expect, in this instance, based on the amplification data for the PRO1281 gene, that the PRO1281 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1281 proteins and nucleic acids have utility in the diagnosis of cancer. Applicants also argue that Hanna and Mornin teach that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma and that the diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by 1HC).

These arguments, including the Declaration by Dr. Polakis, have been considered, but are not deemed persuasive. First, the Examiner's position that an increase in nucleic acid copy number is not predictive of a similar association for protein is supported by the prior art. Therefore, the art does not convincingly recognize that protein levels are increased when gene amplification occurs. For example, Pennica et al. (PNAS 95:14717-14722, 1998) teach that WISP1 and WISP2 are both amplified in tumors, but RNA expression of WISP2 was *reduced* in 79% of tumors, while that of WISP1 was *increased* in 84% of tumors (see abstract). See also Konopka (Proc. Natl. Acad. Sci. 83:4049-4052, 1986), who state that "protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Finally, see Haynes et al. (Electrophoresis 19:1862-1871, 1998), who studied more than 80 proteins relatively homogeneous in half-life and expression level and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that gene amplification, or increased transcription, results in increased protein levels. Accordingly, the showing that the DNA encoding PRO1281 is present in increased copy number

in a particular tumor type is not sufficient to establish any utility for the protein encoded thereby. These references cited by the Examiner are not intended to be a new grounds of rejection, but solely to support the Examiner's position in rebutting Applicants' arguments regarding DNA amplification as a utility. Regarding Hanna and Mornin, they teach the HER-2/neu gene, which has not been shown to encode PRO1281. In view of the prior art presented by the Examiner, the data taught by Hanna and Mornin is also not persuasive since it difficult to extrapolate data from one protein, or its encoding gene, to another.

Applicants further argue that, according to the Declaration by Dr. Ashkenazi, filed under 37 CFR 1.132, "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment." The Declaration further states that "parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy...crucial information for the practicing clinician."

The arguments presented in the Declaration by Dr. Ashkenazi have been considered, but are not deemed persuasive. The fact that a particular gene is not amplified, in the absence of further supporting evidence from Applicants, does not provide a specific and substantial utility, or a well-established utility for that DNA. All it demonstrates is that that particular DNA is not involved in that particular cancer. Similarly, the argument that these genes may enable more accurate tumor classification is also not persuasive, as Applicants have not demonstrated how the genomic DNA for PRO1281 fits into this equation, (i.e. what specific and substantial information it will provide). Any genomic DNA can be used for this purpose since all DNA levels will either increase, decrease, or remain the same. Therefore, in the absence of further information regarding PRO1281, the idea that DNA levels may remain constant does not provide a specific and substantial utility, or well-established utility for the DNA encoding PRO1281. In addition, while the entire wealth of information regarding gene amplification as a whole may be useful, a single genomic DNA itself, such as the one disclosed in this invention for PRO1281, is likely not useful. **Regardless, the claims are drawn to the protein, not the DNA**. Even, *arguendo*, mRNA expression was correlated to PRO1281 gene amplification, or that this DNA could somehow enable more accurate tumor classification does still not provide a utility for the protein of PRO1281 since no information regarding altered expression of PRO1281 protein is disclosed in the specification. Finally, a cancer cell in which the gene did not amplify (i.e. "absence of gene product over-expression") would be expected to have the same protein expression as non-cancerous cells. For this reason, there would be no utility for the protein in the detection of cancer since this protein could not be used to distinguish between cancerous

and non-cancerous cells. Therefore, Applicants have not demonstrated a public benefit for the protein of the present invention. It is believed that all pertinent arguments have been addressed.

6. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. Claims 119-126 and 129-131 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 4 of the Office Action dated 3/9/04 as well as for the reasons given in the above rejection under 35 USC 101. Applicants argue that the claimed invention is enabled because it has utility as argued previously. Applicants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above.

B. The rejection of claims 119-126 and 129-131 under 35 USC 112, first paragraph, have been withdrawn in view of the fact that the appropriate information regarding the ATCC Deposit has been disclosed on page 566 of the specification.

C. Claims 119-126 and 129-131 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 4-5 of the Office Action dated 3/9/04. The part of this rejection relying on the term "extracellular domain" has been withdrawn in view of Applicants' cancellation of this term from the claims. Regarding the remaining part of the rejection, Applicants argue that the claims have been amended to include the functional limitation "wherein said nucleic acid is amplified in colon tumors." They argue that, based on the utility for the PR01281 gene and the nucleic acids encoding the polypeptides in the diagnosis of colon cancer, the skilled artisan would not require undue experimentation to make and use the claimed invention.

These arguments have been considered, but are not deemed persuasive. First, the arguments regarding the utility of the PRO1281 gene and the nucleic acids encoding the polypeptides in the diagnosis of colon cancer is not deemed persuasive as seen in the above rejection under 35 USC 101. Furthermore, the functional limitation recited in the claims is drawn to the nucleic acid molecules, whereas the claims are drawn towards the protein. Applicants' amendments to the claims to recite functional language for the nucleic acid molecules has not enabled the artisan to use the encoded protein. Applicants have not provided any guidance or working examples of any protein encoded by DNA which has been amplified in colon tumors, including PRO1281. Respectfully, simply providing a functional limitation in the claims with regard to the DNA would not allow the artisan to make (e.g. one which has at least 80% amino acid sequence identity to SEQ ID NO:326), or use a protein which meets the limitations

of the claims. In other words, it would not be predictable to the artisan how either identify or make a protein encoded by DNA which is amplified in colon tumors.

Thus, it remains that the complexity and unpredictability of the nature of the invention and art in terms of the diversity of proteases and lack of knowledge about function(s) of encompassed polypeptides structurally related to SEQ ID NO:326, the lack of direction or guidance for using polypeptides that are not identical to SEQ ID N0:326, and the breadth of the claims for structure without function with regards to the claimed polypeptides, would require undue experimentation to use the invention commensurate in scope with the claims. It is believed that all pertinent arguments have been addressed.

7. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 119-126 and 129-131 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 5-6 of the Office Action dated 3/9/04. Applicants have recited the legal standard for written description and argue that whether Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art and the teaching provided by the specification. Turning to Applicants' arguments, they argue that the level of skill in the art is very high and that based on the detailed description of the cloning and expression of variants of PRO1281 in the specification, the description of the gene amplification assay and description of testing the ability of test variant polypeptides in the assay, the actual reduction to practice of sequence SEQ ID NO:326 and the functional recitation in the instant claims, Applicants submit that one of skilled in the art would know that Applicants possessed the invention as claimed in the instant claims.

These arguments have been considered, but are not deemed persuasive. Regarding the legal standard, the teachings provided by the specification, respectfully, demonstrate that Applicants were not in possession of the claimed invention as of the effective filing date. The general knowledge and level of skill in the art do not supplement the omitted description because specific guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus (i.e. of the protein, and not of their encoding DNA), and because the genus is highly variant, SEQ ID NO:326 (which Applicants inadvertently refer to as SEQ ID NO:314 in their response as well) alone is insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Applicants' arguments that numerous variants of PRO1281 (SEQ ID NO:326) were cloned and expressed is also not persuasive since

the specification has not demonstrated that the DNA encoding these variants is amplified in colon tumors, nor that the description of the gene amplification system is sufficient to extrapolate to the claimed proteins (see the rejection above under 35 USC 101). Furthermore, the functional limitation now recited in the claims is drawn to a function of the DNA, whereas the claims are drawn toward proteins encoded by this DNA. Thus, Applicant was not in possession of the claimed genus at the time the invention was made. It is believed that all pertinent arguments have bee addressed.

8. Claim Rejections - 35 USC § 112, second paragraph

A. The rejection of claims 119-126 and 129-131 under 35 USC 112, second paragraph, has been withdrawn in view of Applicants' amendments to the claims to delete the phrase "extracellular domain."

9. Claim Rejections - 35 USC § 102

A. Claims 119-126 and 129-131 remain rejected under 35 USC 102(b) for the reasons already of record on page 7 of the Office Action mailed 3/9/04. Applicants argue that they have made a proper assertion of priority based on U.S. Provisional Application 60/141,037, filed June 23, 1999 for this application and believe they are entitled to this date based on the discussions above. Accordingly, Applicants submit that Baker et al. is not prior art and hence, this rejection should be withdrawn.

This argument has been considered, but is not deemed persuasive for the reasons discussed in Section 2 ("Priority") of this Office Action. Again, the effective filing date for claims 119-126 and 129-131 remains 11/14/01 since Applicants' arguments regarding the gene amplification assay as a demonstration of patentable utility are not persuasive, as seen in the above rejection under 35 USC 101. Therefore, Applicants do not receive priority to U.S. Provisional Application 60/141,037, filed June 23, 1999. Therefore, Baker remains as prior art under 35 USC 102(b).

10. Other Pertinent Art

A. Applicants' arguments regarding Tang et al. and Weimann et al. have been considered. The Examiner agrees that these references are not prior art against the claimed invention for the reasons argued by Applicants as well as for the reasons stated by the Examiner on pages 7-8 of the Office Action mailed 3/9/04. The Examiner's intention in citing these references was simply for Applicants' interest.

11. Conclusion

A. No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961.

Official papers filed by fax should be directed to (703) 872-9306. Fax draft or informal communications with the examiner should be directed to (571) 273-0888.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-0700.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
July 23, 2004

ROBERT LANDSMAN
PATENT EXAMINER